

The Metabolic Effects of Mineralocorticoid Receptor Antagonists in Heart Failure Patients

Alexander E. Berezin*

*Consultant of Cardiology Unit, Internal Medicine Department, State Medical University, Ukraine

Abstract

Heart failure (HF) remains a leading cause of cardiovascular morbidity and mortality worldwide. Mineralocorticoid receptor (MR) antagonists (spironolactone and eplerenone) have been studied in HF patients and in patients with acute coronary syndrome or post-myocardial infarction and left ventricular (LV) dysfunction, as well as hypertensive subjects without HF symptoms. It has suggested that mineralocorticoid receptor antagonists provide cardiovascular protection beyond its diuretic and potassium-sparing capacities. Traditionally, progression of HF relates with not full blockade of renin-angiotensin system (RAS) activation and with so called “escape” phenomenon of neurohumoral activation from effects of angiotensin converting enzyme / angiotensin receptor blockers and beta-adrenoblockers. Circulating and local aldosterone over production is discussed a main cause of none adequate effect of RAS blockade contributed negative cardiovascular remodelling and worse survival. During the last decade, several studies have shown that completed control for RAS activation might be achieved through adding MR antagonists in contemporary treatment scheme. This approach raises survival and leads to a trend in declined mortality rate in patients with HF various etiologic causes. Therefore, there are increasing evidence that both MR antagonists spironolactone and eplerenone might have a different metabolic effect in HF patients and that this difference is required to pay attention in creating of optimal HF therapeutic program. The aim of the mini review is to evaluate clinically significance of metabolic effects of mineralocorticoid receptor antagonists in HF patients.

Keywords: Mineralocorticoid receptor antagonists; Heart failure; Cardiovascular remodelling; Metabolic effects; Tissue repair

Introduction

Heart failure (HF) remains a leading cause of cardiovascular (CV) morbidity, hospitalizations, and deaths [1]. The burden of HF increases in age-related manner and frequently it associates with pre-existing CV disease, i.e. myocardial infarction, cardiomyopathies, and common risk factors, such as hypertension, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, obesity, etc. [2-4]. Through shared CV diseases, CV risk factors and pathophysiological mechanisms of development of HF, chronic blockade of underlying hyperactivity of both sympathetic and renin-angiotensin (RAS) systems is considered a key factor to improve survival among patients with HF originated due to different aetiologies [5]. Indeed, angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) have been demonstrated multiple beneficial effects on survival associated with prevention of target organ damages. There are evidences regarding cardioprotective, cerebroprotective, nephroprotective, angioprotective properties as well as favourable metabolic and antiarrhythmic effects of these drugs. In some clinical settings, especially HF (as ischemia, as well as none ischemic origin), combined therapy ACE-I / ARBs with beta-adrenoblockers are optimal to improve survival, reduce mortality rate and prevent cardiovascular and HF-related complications. However, among HF subjects double blockage of the RAS activity frequently associated with loss efficacy that was described as “escape” phenomenon, which predominantly related with increased circulating and local aldosterone production. It has been postulated that forced continued diuretic therapy, inotropic agents, and various comorbidities (diabetes, insulin resistance, hypertension) might be posed as additional reasons for aldosterone over production. Finally, maladaptively activated regulatory mechanisms affected the renin-angiotensin-aldosterone axis and the sympathoadrenal system activity play a pivotal role in increase mortality rate through none adequate control for cardiovascular remodelling, arrhythmogenesis, coagulation,

low-intense inflammation. Therefore, contemporary protocol for treatment and prevention of HF is not completely implemented due to different reasons. In fact, despite modern preventive and treatment cardiology programmes, which are required HF patients, have created according contemporary clinical guidelines and appropriate adapted to medical and cultural settings, less than one-half HF patients are being treated adequately [6].

Current clinical recommendations for treatment and prevention of HF devote adding of MR antagonists to ACE inhibitors / ARBs and beta-blockers as important approach directed improve clinical settings, achieve full control for HF signs and symptoms, prevent cardiovascular remodelling and related with all mentioned above improve survival [7].

Mineralocorticoid receptor (MR) antagonists (spironolactone and eplerenone) have been studied in patients with advanced HF and also in patients with acute coronary syndrome or post-myocardial infarction and left ventricular (LV) dysfunction, as well as hypertensive subjects without HF symptoms [8-10]. However, it has suggested that MR antagonists provide cardiovascular protection beyond its diuretic and potassium-sparing capacities [11]. Little is known about whether MR antagonists are able to reverse tissue remodelling and vascular function especially in HF subjects with comorbidities, i.e. diabetes, obesity, metabolic syndrome [12]. Certain HF-modifying medications

*Corresponding author: Alexander E Berezin, Professor, MD, PhD, Consultant of Cardiology Unit, Internal Medicine Department, State Medical University, 26, Mayakovsky av., Zaporozhye, Ukraine, Tel: +380612894585; E-mail: dr_berezin@mail.ru

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including MR antagonists mitigated CV risk, but it is not clear whether metabolic effects of nonselective aldosterone receptor antagonist spironolactone and selective antagonist eplerenone are similar [13]. The aim of the mini review is to evaluate clinical significance of metabolic effects of MR antagonists in HF patients.

Aldosterone in Heart Failure

Aldosterone has been implicated for many years as an important substance in the pathogenesis of CV disease [14]. Elevated circulating aldosterone has found in patients with asymptomatic and symptomatic HF developed due ischemic and none ischemic causes [15]. Therefore, the pivotal role of aldosterone was found in cardiomyopathies, hypertension, atrial fibrillation, myocardial infarction / acute coronary syndrome, and dysmetabolic states, i.e. diabetes mellitus, hypothyroidism, obesity and insulin resistance. Increased circulation and local level of aldosterone is attributed to hyperactivity of both RAS and sympathetic system. Therefore, in heart failure the main causes of aldosterone level elevation are electrolyte and acid-base abnormalities particularly mediated by diuretic use, exposure of cardiac glycosides, and ACE inhibitors, as well as nature evolution of HF associated with neurohumoral activation (stimulation of the renin-angiotensin-aldosterone system, sympatho-adrenergic stimulation, deficiency of natriuretic peptide system activity, etc.) [16,17]. Local production of aldosterone in heart and vessels induced by angiotensin II is powerful effector for differentiation and growth of fibroblasts, collagen over production, myocyte hypertrophy and altered collagen turnover [18]. It is well known that HF development associates with increased expression of central and peripheral mineralocorticoid receptors. Moreover, cardiac and vascular imbalance between natriuretic peptides and aldosterone, toward increased MR signalling, contributes to adverse cardiovascular remodeling in response to pressure overload, ischemia / reperfusion, inflammation [19]. All these findings explain the innate pathophysiological mechanisms of extracellular matrix remodelling, inducing of oxidative stress, as well as development of endothelial dysfunction via aldosterone-induced pathway [19,20]. In fact, vascular inflammation resulted in aldosterone over production and attenuated by different originated chemo attractants, apoptotic fragments and oxidative stress components plays a pivotal role in tissue injury in CV diseases [21,22]. Overall, aldosterone may lead to controversial metabolic effect on peripheral tissue contributing in tissue repair. Indeed, aldosterone is as one of the main attractant for progenitor cells with angiopoietic and protective capacities and it also may stimulate their migration in dose dependent manner [23]. In this context chronic MR antagonism is discussed a potent pharmacological path for achieving a fulfil control for neurohumoral and low-intense inflammatory activation suitable HF development. Indeed, the role of the MR antagonisms has emerged from experimental studies and has been confirmed in clinical settings including patients with hypertension, ischemic and none ischemic HF, cardiomyopathies, myocardial infarction and atrial fibrillation [24].

Non Selective Versus Selective Mineralocorticoid Receptor Antagonism

Spironolactone as a nonselective aldosterone receptor antagonist realizes a pharmacological effect thereby binding of both types of receptors, i.e central and peripheral aldosterone receptors and steroid receptors. The expected positive effects of spironolactone (stimulation of diuresis, antihypertensive effect, reversal of cardiovascular remodelling, prevention of arrhythmia, anti-inflammatory and anti-apoptotic effects, minimize of infarct and peri-infarct zones, and

related with these improving of clinical outcomes) associate with aldosterone receptor antagonism [25]. In opposite, sex hormone-related adverse effects (gynecomastia) relate to steroid receptor blocking. However, increase of potassium plasma level is common for aldosterone receptor antagonist use [26]. Eplerenone is the first of a new class of drugs known as selective aldosterone receptor antagonists in minimal manner blocked steroid receptors, and thereby minimizing many of the hormonal side effects seen with spironolactone [27]. Overall eplerenone has been demonstrated better profile of safety and tolerability than spironolactone [28]. The antihypertensive efficacy of both drugs are probably similar, but eplerenone shown a significant renoprotective effect in diabetic patients with hypertension [29]. Recently clinical trials have been revealed a significant reduce mortality and cardiovascular morbidity in post-myocardial infarction patients with systolic HF when eplerenone was added to the standard HF therapy [30]. In opposite, for patients with HF and preserved left ventricular ejection fraction (LVEF), spironolactone use was associated with an increase in all-cause readmission probably due to the higher rate of hyperkalemia [31]. Despite these findings, the role of spironolactone use in HF patients with reduced LVEF as a component of HF-modified therapy is confirmed [30]. Moreover, there was no difference in CV event rates with regard to mineralocorticoid receptor antagonists use patterns, independent of galectin-3 concentrations [32]. Interestingly, mineralocorticoid receptor antagonists may effectively treat established obesity-related diastolic HF via blood pressure-independent mechanisms [33]. However, recently results indicated that eplerenone is probably able to prevent the development of HF and metabolic abnormalities better than spironolactone, but patophysiological mechanism the distinguish underlying metabolic effects produced both drugs are still not completely clear.

Metabolic Effect of Mineralocorticoid Receptor Antagonists

Metabolic effects of both mineralocorticoid receptor antagonists affect neurohumoral activity, inflammatory changes, and tissue reparation capacity.

Impact of spironolactone and eplerenone on neurohumoral state in HF patients

Yamaji et al. [13] reported that eplerenone and spironolactone in HF patients led to significantly decrease of plasma B-type natriuretic peptide levels. Therefore, plasma aldosterone levels were significantly increased after 4 months of drug exposure. In patients receiving spironolactone, plasma adiponectin levels were significantly decreased and HbA_{1c} and cortisol levels were significantly increased. In patients receiving eplerenone, there was a significant positive correlation between the change in cortisol and the change in HbA_{1c}. In contrast, in patients receiving eplerenone, changes of circulating adiponectin, HbA_{1c} and cortisol were not found. Authors concluded that the metabolic effect of eplerenone differed from that of spironolactone and that eplerenone had a superior metabolic effect especially on HbA_{1c} in CHF patients [13]. Probably direct comparison between spironolactone and eplerenone in large clinical trial are required.

Effect of mineralocorticoid receptor antagonists on numerous and pattern of circulating bone marrow derived-endothelial progenitor cells

In fact, injured endothelial monolayer is regenerated by circulating bone marrow derived-endothelial progenitor cells (EPCs), and levels of circulating EPCs reflect vascular repair capacity and

severity of endothelial dysfunction [34]. There are hypothesis that mineralocorticoid receptor antagonists may realize a positive effect on restoring of adhesive function, migration, and biological capacities of EPCs [35] and thereby improve vascular integrity and function [36]. Because state of endothelial dysfunction associated with high CV mortality, mineralocorticoid receptor antagonism might be discussed as therapeutic approach contributed to vascular injury repair. Indeed, aldosterone-induced vascular dysfunction may be prevented by adding its selective antagonist eplerenone [23]. Jung C et al. [36] reported that HF patients with ongoing eplerenone use showed significantly higher levels of circulating cells expressing CD34+ and CD34+KDR+ and CD34+CD133+KDR+ cells and that these effects of eplerenone could be shown to be independent of NYHA status, underlying CV morbidity, LVEF and concomitant medication. As an explanation of effect provided eplerenone on angiopoietic EPCs it is suggested that aldosterone could induce translocation of the mineralocorticoid receptors into EPCs and thereby impair their multiple cellular functions, i.e. differentiation, migration, and proliferation [37,38]. Probably, EPCs express mineralocorticoid receptors mediated functional impairment by PKA-dependent increase of reactive oxygen species. The capacity of angiogenic factor (endothelial nitric oxide synthase, vascular endothelial growth factor, angiopoietin-1, and angiopoietin-2) to restore biological function of EPCs may be modulated through mineralocorticoid receptor antagonism by eplerenone use [38]. However, this assumption is contrary to the concept that aldosterone itself capable of inducing biological activity of EPCs [23]. It is still unknown whether spironolactone is useful for restoring of angiopoietic EPC populations in HF patients.

Future Perspectives

Along with the advance of new possibilities to interfere directly with the pathogenesis of the HF, the approach regarding modalities of endogenous reparative capacities and possibilities of co-regulation of this system through MR antagonists appear to be attractive and probably have clinical significance. Large clinical studies are needed to explain the potent role of these findings in treatment of choice of HF patient.

In conclusion, increasing evidence suggests that both MR antagonists spironolactone and eplerenone might have a different metabolic effect in HF patients and that these differences are required to pay attention in creating of optimal HF therapeutic program. Therefore, chronic MR antagonism may provide a novel and probably effective therapeutic approach for the repair of CV diseases, such as HF. Probably contemporary treatment scheme might check the possibilities of eplerenone to modulate metabolic effect regarding vascular endogenous reparative potent.

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